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Study of Bone Mineral Density and Bone Alkaline Phosphatase in Type 2 Diabetic Mellitus Postmenopausal Women in Kerbala.

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Abstract:

Background: The most prevalent metabolic bone disease among postmenopausal women with type 2 diabetes is osteoporosis. Even in those with normal or elevated bone mineral density (BMD), type 2 diabetes is associated with a higher fracture incidence than the non-diabetic population. As a result, the pathophysiology of bone fragility brought on by type 2 diabetes (T2DM) is significantly influenced by bone quality. A decline in BMD that is below normal reference levels but not low enough to satisfy the diagnostic standards for osteoporosis is referred to as osteopenia. BMD is diagnosed via dual-energy X-ray absorptiometry bone scans. An ectoenzyme called bone alkaline phosphatase (BALP) is affixed to the outside of osteoblast cell membranes. It enters the bloodstream in part. About 95% of the total ALP (TALP) activity in human serum is made up of liver ALP and BALP.

Aims: The aim is to determine whether diabetic postmenopausal osteoporosis (diabetic PMOP) and non-diabetic postmenopausal osteopenia have any influence on an increased risk of fracture in diabetic patients, the current study compares the studied results of BALP, Total ALP, BMD, body mass index (BMI), and age.

Materials and Methods: We performed a cross-sectional study in Kerbala medical hospital enrolling 80 subjects, 40 PMOP with T2DM, aged between (51-75) years, and 40 postmenopausal osteopenia without T2DM, aged between (50-74) years. All Patients had been in spontaneous menopause for at least, one year. For each subject we measured BMI, BMD, serum BALP, total ALP and T-scor during November, 2023 to September, 2024. Diabetic patients were collected from Al-Hassan center for Endocrinology and diabetes mellitus and Osteoporosis center at Al- Hassan Medical City, Kerbala Health Directorates, Kerbala/ Iraq. The mean and standard deviation of the parameters of the two groups were computed and compared by unpaired Student's T-test. The relationship between variables was measured by Karl Pearson's correlation coefficient. A statistical significance is set at a 5% level of significance ($P < 0.05$).

Result: Age and TALP were significantly higher in diabetic PMOP compared with non-diabetic osteopenia (62.8 ± 6.8 vs. 56.4 ± 7.37 year), (227.43± 61.46 vs. 201.50 ± 41.47 U/L), $P<0.05$. BMI was non-significant in diabetic PMOP compared with non-diabetic osteopenia (29± 4.72 vs.30.34 ± 4.64 kg/m^2) $P>0.05$. BMD was significantly lower in diabetic PMOP compared with non-diabetic osteopenia (0.72 ± 0.06 vs. 0.86 ± 0.04 g/cm^2) $P<0.05$. BALP was non-significantly higher in diabetic PMOP compared with non-diabetic osteopenia (52.33 ± 11.62 vs. 49.51 ± 7.64 ng/L) $P>0.05$. BMD of diabetic PMOP and non-diabetic osteopenia showed a non-significant negative correlation with BALP and TALP. T-scor was significantly lower in diabetic PMOP compared with non-diabetic osteopenia (-3.04 ± 0.45 vs. -1.64 ± 0.38) $P <0.05$.

Conclusions: Type 2 diabetic PMOP have BMD lower than the non-diabetic osteopenia. Low BMI in diabetic PMOP is an indicator for osteoporosis and its related fracture. In diabetic PMOP, T-scor is only predict by high level of BALP and TALP. Low levels of BALP and TALP are the predictors of T-scor in non-diabetic osteopenia.

Keywords: Osteoporosis, PMOP, T2DM, BALP, TALP.

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Introduction:

With the greatest incidence rates among postmenopausal women, osteoporosis is a growing worldwide health concern. Increased bone fragility and fracture susceptibility are the results of osteoporosis, a systemic bone disease marked by osteopenia and altered bone microstructure **(Coll, *et al.*, 2021),(Gao, S., *et al*,2023)**.Through the use of a particular radiological test known as bone mineral densitometry, the World Health Organization (WHO) defines it primarily in women as "the presence of a BMD less than or equal to -2.5 standard deviations below the average bone mass of healthy 20-year-olds." **(Elonheimo, *et al.*, 2021)**.The risk of osteoporosis in women is approximately 3 times higher than in men **(Noh *et al.,* 2018),(Lorentzon, M.,*et al*,2022)**. Elderly people's quality of life is significantly impacted by osteoporosis and fractures, which can cause significant financial and emotional strain on patients and their family. The fundamental cause of all osteoporosis is an imbalance between bone resorption and bone growth **(Cai,Dong *et al.*, 2021).** As a direct result of this disease, women are more likely to experience bone fractures because, when pregnant and lactating, the body attempts to reduce the calcium stores in the bone due to dietary calcium and vitamin D deficiencies, which results in a progressive loss of bone mass. Because of this, it appears later and more commonly in women who are amenorrheic or post-menopausal, who also have other hormonal abnormalities that impact bone metabolism, such as a reduction in the ovaries' synthesis of estrogens **(Kim, *et al.*, 2020),(Kuliczkowska-Płaksej, J.,*et al*,2024)**.T2DM affects bone metabolism and strength by influencing osteoblast and osteoclast. The imbalance between osteoblast and osteoclast might cause osteoporosis **(Sassi, *et al.*, 2018)**. Additionally, T2DM may alter the quantity and quality of bone, changing the structural characteristics of bone mass. T2DM is thought to be the cause of associated fractures because it alters bone homeostasis. The most significant predictor of osteoporotic fractures is BMD, and the gold standard for diagnosing osteoporosis has been dual-energy X-ray absorptiometry (DXA)-based BMD. BMD based on (DXA) is essential for managing osteoporosis and osteopenia and evaluating fracture risk **(Ferrari, *et al*., 2018)**,**(Martiniakova, M.,*et al,*2024)**. Bone metabolism in diabetes is influenced by many factors, including depressed osteoblast activity and decreased numbers of osteoclasts “sweet bones” as a result of abnormal insulin secretion and/or insulin action. Insulin-like growth factors and other osteoclastogenic cytokines are also implicated **(Xu, 2021)**. Increased osteoclastic bone resorption in women is directly linked to the sudden drop in blood estrogen levels during menopause. In postmenopausal women, low estrogen levels cause circulating macrophages to release osteoclastic cytokines, which in turn activate RANK and encourage the activation of osteoclasts. Furthermore, osteoclast longevity is prolonged when the direct pro-apoptotic actions of estrogens on osteoclasts are eliminated, which speeds up trabecular bone loss **(Golden, 2020)**. The clinical term "osteopenia" refers to a reduction in BMD that is below normal reference values but not low enough to satisfy the diagnostic requirements for osteoporotic status. DXA bone scans are used to diagnose BMD. WHO defines osteopenia as a T-score between -1 and -2.5, with results below -2.5 indicating osteoporosis**(Porter, 2022)**. The hydrolysis of phosphate monoesters, such as inorganic pyrophosphate (PPi), is catalyzed by the ubiquitous enzyme alkaline phosphatase (ALP), a membrane-bound glycoprotein. Bone ALP (BALP) is a homodimer that is attached to matrix vesicles and osteoblast membranes. Soluble (anchor-free) BALP is released into the bloodstream during phospholipase cleavage and can serve as a biomarker of bone formation. In order for BALP to break down PPi, an inhibitor of the production of hydroxyapatite, which is present in the extracellular matrix, it must be attached to the outside of the matrix vesicle membrane **(Nizet, *et al.,* 2020)**.

With the aim to determine if diabetic postmenopausal osteoporosis and non-diabetic postmenopausal osteopenia have any factors that enhance the risk of fractures in diabetic patients, the current study compared BALP, Total ALP, BMD, T-scor, BMI, and age.

Materials and Methods:

This cross-sectional study was performed in Kerbala medical hospital during November,2023 to September,2024 by enrolling totally 80 subjects, 40 PMOP with T2DM with age ranged between (51-75) years, and 40 postmenopausal osteopenia without T2DM with age ranged between (50-74) years. All Patients had been in spontaneous menopause for at least, two year. In each subject we measured serum BALP which determined by Sandwich ELISA technique, serum TALP which was analyzed by chemistry analyzer smart 120T/H, deionized water was used as a blank solution, BMI was directly measured for each patients, BMD and T-scor by

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Dual energy x-ray absorptiometry scan (DEXA) at lumbar spine regions (L1–L4 vertebrae) confirmed postmenopausal osteoporosis were included. Diabetic patients were collected from Al-Hassan center for Endocrinology and diabetes mellitus and Osteoporosis center at Al-Hassan Medical City, Kerbala Health Directorates / Kerbala-Iraq. Inclusion criteria were as follows only patients with postmenopausal osteoporosis women and age of female ≤ 50 year and T2DM patients that have duration ≤ 5 year were enrolled in the present study.

Exclusion criteria were as follows individuals with a history of medication for the treatment of PMOP or medication known to affect bone metabolism within 6 months. Patients with diseases known to affect bone metabolisms, such as severe malabsorption syndrome, chronic liver disease, inflammatory bowel disease, primary hyperparathyroidism that is not effectively controlled, hypercalcemia, Paget's bone disease, active kidney stones, osteogenesis imperfecta, and pituitary disease. Women were identified with surgical menopause, hypertensive, hormone replacement therapy and type 1 diabetic mellitus women were excluded from the study. Patients with secondary osteoporosis, such as rheumatoid arthritis, Patients who have continuously received calcitonin, estrogen, corticosteroids, calcitriol, and other drugs that can change bone metabolism within 3 months. Patients with severe liver and kidney diseases, peptic ulcers, immune diseases, malignant tumors, any type of thalassemia disease. Patients with factors that affect the measurement results of BMD, such as the history of lumbar spine fixation surgery, ankylosing spondylitis and amputation surgery, and bone fracture were excluded. Diagnostically confirmed cases of postmenopausal osteoporosis attending the osteoporosis unit. All the cases were evaluated and selected by simple random technique after fulfilling the selection criteria. The cases of osteoporosis were reported to the unit of osteoporosis. After finding the suitability as per selection criteria, they were requested to participate in the study and briefed about the nature of the study and interventions used. Informed consent was obtained. The consented patients were enrolled in the study. Further descriptive data of the participants like name, age, sex, and detailed history, were obtained by interviewing the participants and were recorded on a predesigned and pretested proforma. BMD was determined by a diagnostic medical system Stratos Bone Densitometry equipment was designed and manufactured in France. The instrument operation and data interpretation were made according to manufacturer instructions. The interpretation was made according to BMD status, which was categorized as Osteoporotic (T-scor at or below -2.5), (osteopenic T-scor between -1 and -2.5), and normal (T-scor at above -1) postmenopausal women. Height and weight were measured at the time of DEXA measurement and body mass index (BMI) was calculated as the weight divided by the square of the height (kg/m^2). Five ml of blood sample was obtained by venipuncture from each patient during the morning (9-11 a.m.) and drawn into a gel tube, then allowed to stand at room temperature till the clot was formed. The blood tube was centrifuged, and serum was separated within 2 hours by centrifuging at 4,000 rpm for 10 min. All samples were stored in nonvacuum sterile tubes at −20 °C till further analysis. Serum TALP, was measured by an automatic analyzer smart 120T/H, (GenoLAB Tech, USA). Serum BALP was measured by the enzyme linked immunosorbent assay technique, PARS BIOCHEM KIT (BIOTEK, USA). The data were analyzed by IBM Corp, and released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Mean and standard deviation of the parameters of the two groups were computed and compared by unpaired Student's T-test. The relationship between variables was measured by Karl Pearson's correlation coefficient. A statistical significance is set at a 5% level of significance ($P < 0.05$).

Results:

Bone mineral density and T-scores were evaluated in 40 types 2 diabetics' postmenopausal osteoporosis women and 40 non-diabetic postmenopausal osteopenia women. Table 1 shows the Mean and Standard Deviation (SD) of Age, BMI, T-scor, BMD, BALP, and TALP. Age and Total ALP (TALP) were significantly higher in diabetic PMOP compared with non-diabetic osteopenia. BMI was non-significant low in diabetic PMOP compared with non-diabetic osteopenia. T-scor was significantly lower in diabetic PMOP compared with non-diabetic osteopenia. BMD was significantly lower in diabetic PMOP compared with non-diabetic osteopenia. Bone ALP (BALP) was non-significant higher in diabetic PMOP compared with non-diabetic osteopenia while TALP was a significant higher in diabetic PMOP compared with non-diabetic osteopenia. BMD of diabetic PMOP showed a significant very strong positive correlation with T-scor while BMD in non-diabetic osteopenia showed a significant strong positive correlation with T-scor. BALP and TALP of diabetic

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PMOP and non-diabetic osteopenia showed a non-significant negative correlation with BMD. Diabetic Mellitus duration showed a significant very strong negative correlation with BMD.

Table 1: The mean ± SD of the observed parameters determined in diabetic PMOP and non-diabetic osteopenia.

Parameters	Reference Range	Total N = 80 Mean ± SD	Diabetic PMOP N = 40 Mean ± SD	Non- Diabetic Osteopenia N = 40 Mean ± SD	P.Value
Age, Year	-----	59.6 ± 7.75	62.8 ± 6.81	56.4 ±7.37	<0.0001*
BMI, kg/m^2	-----	29.66±4.7	29.0 ± 4.72	30.34 ± 4.64	0.166
Bone Mineral Density, g/cm^2	-----	0.79 ± 0.09	0.72 ± 0.06	0.86 ± 0.04	< 0.0001*
T-scor	> -1	-2.34 ± 0.82	-3.04 ± 0.45	-1.64 ± 0.38	< 0.0001*
TALP. U/L	98 - 279	214.45 ± 53.7	227.43 ± 61.46	201.5 ± 41.47	0.023*
BALP, ng/L	7.5 - 135	50.92 ± 9.88	52.33 ± 11.62	49.51 ± 7.64	0.180

***P<0.05 ; SD: Standard Deviation ; BMI: Body mass index ; BMD: Bone mineral density**

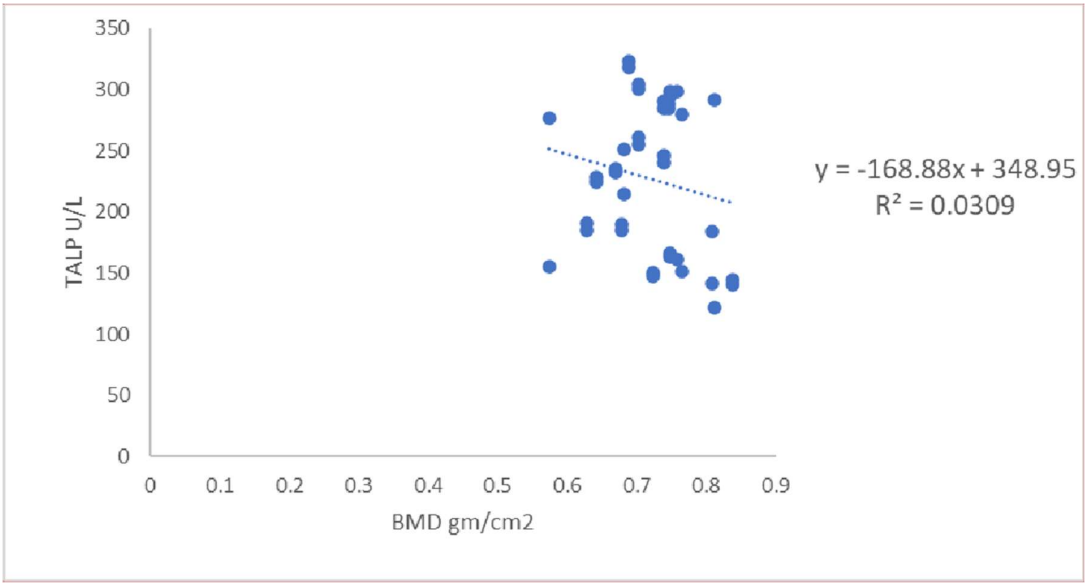

Fig 1: Correlation between BMD with TALP in diabetics PMOP.

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Table 2: Relationship between Age, T-scor, BMI, BMD, Serum BALP and TALP in postmenopausal (diabetic Osteoporosis and non-diabetics Osteopenia).

Correlation between parameters	Diabetics Osteoporosis		Non-diabetics Osteopenia	
	r	Sig.	r	Sig.
Age and T-scor	0.107	0.512	-0.388*	0.013
Age and BMI	0.093	0.568	-0.616**	<0.01
T-scor and BMI	0.405**	<0.01	0.488**	<0.01
T-scor and BMD	0.969**	<0.01	0.676**	<0.01
T-scor and BALP	-0.142	0.381	-0.081	0.621
T-scor and TALP	-0.098	0.548	-0.335*	0.035
BMI and BMD	0.375*	0.017	0.255	0.112
BMD and BALP	-0.161	0.322	-0.142	0.382
BMD and TALP	-0.176	0.278	-0.218	0.176
Duration of DM and T-scor	-0.820**	<0.01		
Duration of DM and BMD	-0.810**	<0.01		

***Statistically significant at p <0.05 level (two-tailed) ; **Statistically significant at p < 0.01**

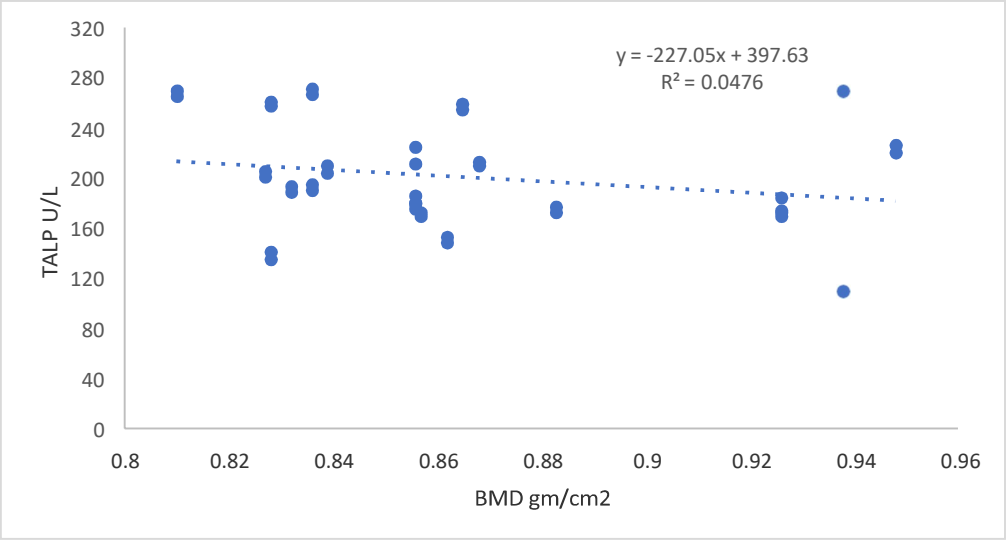

Fig. 2: Correlation between BMD with TALP in non-diabetics osteopenia

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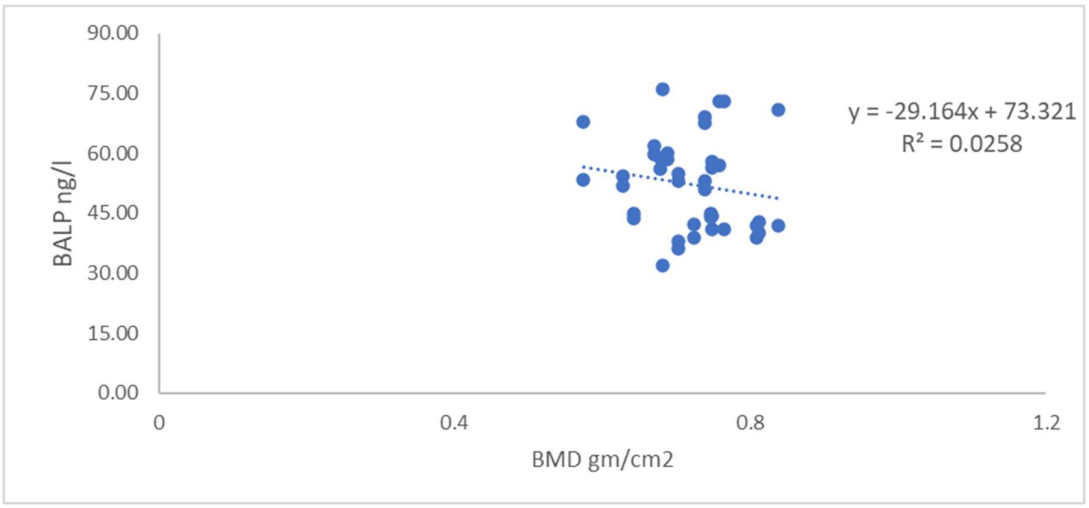

Fig. 3: Correlation of BMD with BALP in diabetics PMOP

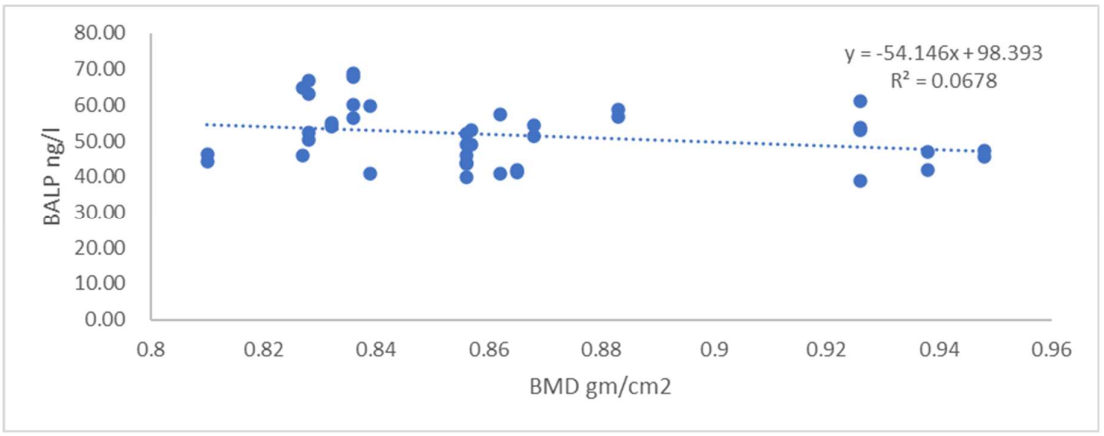

Fig. 4: Correlation of BMD with BALP in non-diabetics osteopenia

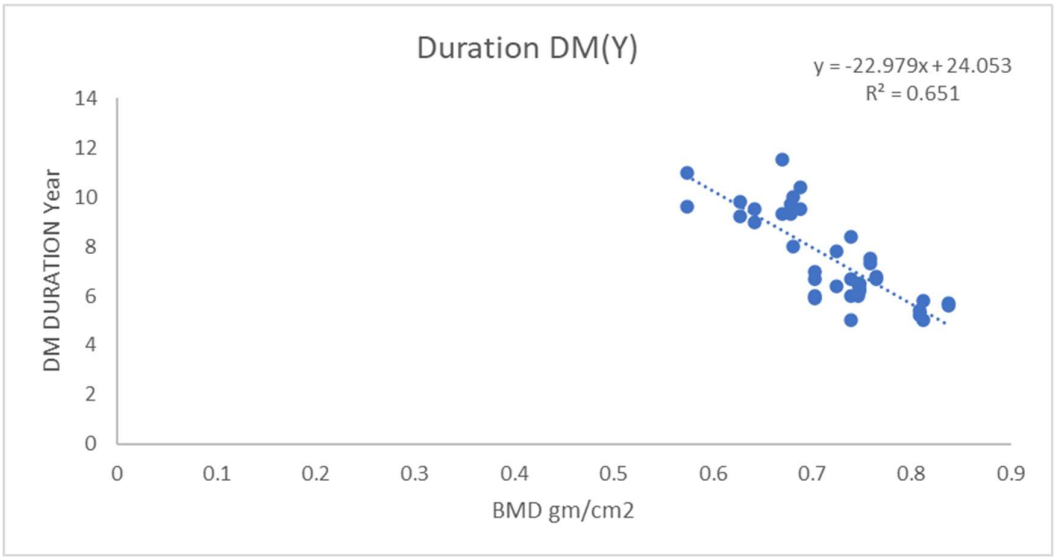

Fig. 5: Correlation of BMD with duration of diabetics PMOP

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Discussion:

We showed in this study the negative effect of DM duration on the BMD, this agree with study done by **(Jang, *et al.*, 2018).** The mean duration of diabetes among cases was 7.5 years . In diabetic PMOP, the BMD was significantly lower as compared with non-diabetic osteopenia. A significant positive correlation was found by others between BMD and body mass index in diabetic PMOP and a non-significant result was obtained in non-diabetic osteopenia group **(Polyzos, *et al.*, 2021**). Serum alkaline phosphatase activity levels were significantly higher in diabetic PMOP as compared with non-diabetic osteopenia groups which also in agreement with other study **(Chen, *et al*., 2017 and Lim,*et al.,* 2020)**.This may be due that ALP can be drain from osteoblast which is rich with its activity also it found in plasma membrane of the cell in the liver, intestine, and placenta, all of which may contribute to the total amount of alkaline phosphatase **(Lim,*et al*., 2020)**. The age was significantly higher in diabetic PMOP as compared with non-diabetic osteopenia groups which also in agreement with other study **(Wen, *et al*., 2021)**. BMI was non-significant higher in non-diabetic osteopenia compared with diabetic PMOP groups **(Wen, *et al.*, 2021)**.

Moreover, several studies demonstrated the relationship between low BMI, low bone mineral density levels, and the risk of osteoporotic fractures (Li, H. L.,2024), and some studies found that increased BMI is associated with elevated BMD levels and a reduced risk of fractures due to osteoporosis**(Chen,R., *et al.,*2024)**. Further studies are needed to explore the relationship between BMI and BMD levels, especially among older diabetic women patients. Previous studies concluded that when BMI increases, BMD levels will also increase, which further supports our findings **(Doğan, *et al.*, 2010),(Cao, X., *et al*,2023)**.The data of this study showed decrease BMI and BMD in diabetic osteoporosis as compared with non-diabetic osteopenia groups and this corresponds to the positive relationship between BMI and BMD and may be high mean of BMD and BMI in diabetic osteoporosis patients and this confirm positive correlation between BMD and BMI**.** Other studies explained that such relationship exists because heavy body weight could result in bone remodeling to compensate for the heavy mechanical load **(Kang, *et al*., 2014)) Hart, N. H.,*et al.,2022)***. Another study suggested that an increased BMI could subsequently increase the levels of leptin, which contributes to the relationship by promoting osteoblast production and functions **(Russell, *et al.*, 2010).** In this study, a negative association was observed between the duration of diabetes and BMD. These results were consistent with other findings performed by various works**(Kao, *et al.*, 2003).**

They demonstrated that the duration of diabetes as a risk factor for decreased BMD in T2DM subjects. However these findings were against the observation of **(Yao,** X.,***et al.,*2020)**who found no significant relationship between BMD and the duration of diabetes. Type 2 diabetes has been recognized as an independent risk for fragile fractures **(Neglia, *et al.*, 2016)**. The high fracture risk in T2DM patients can be induced by hypoglycemia, muscle weakness, and chronic complications (such as retinopathy and neuropathy) which usually happen in a patient with a longer duration of T2DM **(Majumdar, *et al.*, 2016).** However, hyperglycemia should always be kept in mind because it plays a vital role in the impaired bone metabolism in T2DM patients, leading to reduced bone strength **(Napoli, *et al.*, 2017).** Hyperglycemia causes calcium homeostasis imbalance by inhibiting the bone formation and accelerating bone resorption. Increased osteoblast apoptosis induced by high glucose has been demonstrated **(Wu, *et al.*, 2016).**The loss of BMD in osteoporotic group was supported by the increased activity of ALP **(Macdonald, *et al.*, 2004).**

The study showed raised levels of BALP in osteoporotic patients as compared to osteopenic group, and these high levels may be associated with prevalent vertebral fractures and higher levels of ALP were related with reduced T-scores which showed an imbalance between osteoblastic and osteoclastic activity shifting the equilibrium towards increase osteoclastic activity and in diabetic groups BALP levels could increase the risk of osteoporosis **(Biver, *et al*., 2012 and Wen, *et al*., 2021).** Serum ALP is a clinical marker of bone metabolism, and its activity arises from the bone and liver. The ALP level of the diabetic osteoporosis and non-diabetic osteopenia groups was significantly different. ALP elevation has been commonly seen in patients with bones diseases and/or renal hyperfiltration **(Oh, *et al.*, 2015),** they have been associated with diabetic patients. In particular, renal hyperfiltration has been observed in patients with newly diagnosed type 2 diabetes **(Penno, G., *et al.,*2020)**. However, further investigations on the causal effects of ALP level on the development of diabetes are needed **(Chen,Tsai *et al.*, 2017)**. This study found that diabetics and non-diabetic groups showed a non-

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significant negative correlation between BMD and ALP. BALP is an enzyme that promotes bone mineralization by inactivating pyrophosphate and osteopontin, which are both inhibitors of bone mineralization. ALP and BALP measurements were widely recommended, to evaluate not only the bone mineral status disorder but also the rate of vascular calcification **(Akin, *et al.*, 2003 ; Buchet, *et al*., 2013 and Baralić, *et al.*, 2019).** Low BMD levels in diabetic osteoporosis compared with non-diabetic osteopenia was in agreement with others **(Forst, Beyer *et al.*, 1995 and Kwon, *et al.*, 1996)**.

Conclusions:

Type 2 diabetic PMOP has BMD lower than non-diabetic osteopenia. ALP activity level was the strongest predictor of T-score. Elevated serum ALP levels may help in determining loss of BMD in postmenopausal females.

Diabetic patients with low BMI and BMD possibly have a high risk of osteoporosis than those with high BMI and BMD. All patients with diabetes should be encouraged and educated about controlling their diabetes and maintaining normal BMI or increasing BMI for those with low BMD by having well-balanced and healthy diets to prevent the risk of fragility fractures and osteoporosis. The BMD had a strong negative correlation with the duration of diabetes; additional studies are warranted to understand the decreasing BMD among T2DM patients more thoroughly to prevent fractures and their subsequent deleterious consequences on individuals with diabetes. In diabetic group BALP, TALP levels could increase the risk of osteoporosis. There is a negative correlation between BMD and ALP in non-diabetic osteopenia. Therefore, the measurement of ALP can provide supplementary data as an early predictive marker for osteoporosis.

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